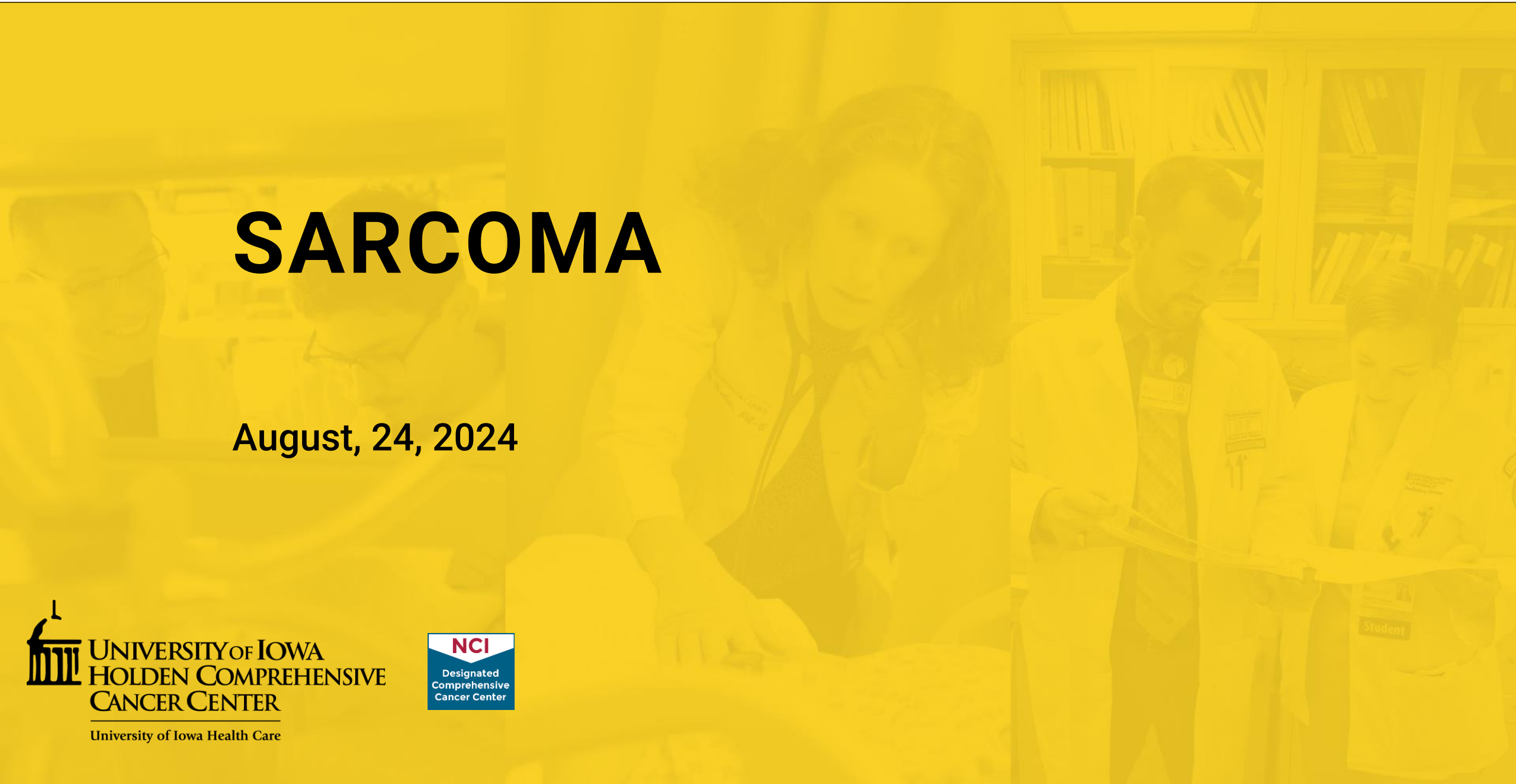
SARCOMA

August, 24, 2024



University of Iowa Holden Comprehensive Cancer Center

University of Iowa Health Care

NCI Designated Comprehensive Cancer Center

Disclosures

- Sponsored Research- Cogent Biosciences, Inc.
- Sponsored Research- Ascentage Pharma Group, Inc.
- Advisory Board: Deciphera Pharmaceuticals

SARCOMA

- “A riddle wrapped in a mystery inside an enigma”
- Very challenging to study and understand
  - Derived from mesenchymal stem cells (behave differently from carcinomas)
  - Rare (1% of all malignancies), do difficult to accrue patients
  - >150 different subtypes, each with a unique biology
  - Classification system is a mess
  - Very difficult to classify (frequently the diagnosis changes when transferring the pathology), and disagreement among pathologists
  - Naming conventions change frequently
- Research is ongoing to better understand these malignancies

Lete-cel in Patients With Synovial Sarcoma or Myxoid/Round Cell Liposarcoma: Planned Interim Analysis of the Pivotal IGNYTE-ESO Trial

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- 20. MRCPI MBBCh. University Health Network – Princess Margaret Cancer Centre, Toronto, ON, Canada;

Background Information

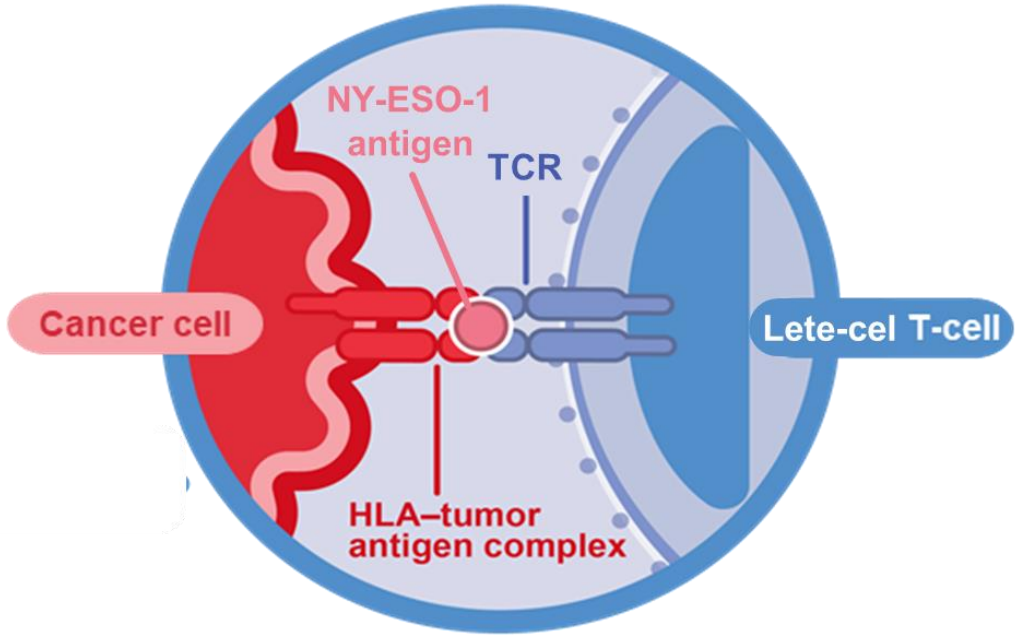
- Synovial Sarcoma and myxoid/round cell liposarcoma about about 5-10% of all STS[1]
- Synovial sarcoma and myxoid/round cell liposarcoma are promising targets of cellular therapied due to expression of NY-ESO-1 (65% and 80-90% respectively)[3,4] and MAGE-A4[3]
- Both are initially sensitive to chemotherapy, but metastatic disease is generally incurable outside of select cases
- Both treated in the Phase II trial of afami-cel, a TCR T-cell therapy targeting MAGE-A4[2]

[a]MAGE-A4 expressed in ~82% of SyS and ~68% of MRCLS.[6]

1. De Vita A, et al. *Onco Targets Ther*. 2016;9:6233–46. 2. D'Angelo SP, et al. *Lancet*. 2024;403:1460–71 3. Iura K, et al. *Virchows Arch*. 2017;471:3837–92. 4. Endo M, et al. *Mod Pathol.* 2015;28:587–95.

Letetresgene Autoleucel

- Lete-cell is a product containing autologous CD4+ and CD8+ T cells genetically modified to express TCR recognizing NY-ESO-1 peptide via HLA-A*02 subtypes
- Infused following lymphodepletion



IGNYTE-ESO Study Design

- Ongoing international, open-label Phase 2 trial (NCT03967223)
- Eligibility
  - HLA-A*02:01, *02:05, or *02:06 phenotypes
  - Age ≥ 10 years
  - NY-ESO-1 espressing (≥30% staining at 2+/3+ per IHC)
  - ECOG 0-1
  - Must have had anthracycline
  - Must have progressed on prior line of therapy and have measurable disease per RECIST v1.1
- Endpoints: ORR per RECIST v1.1 via central independent review
  - Secondary endpoints: Safety, ORR per investigators, time to response, disease control rate, PFS, OS
- Interim analysis: if ≥ 14 of 45 patient have a response at 6 months, then success would be met
- As of presentation, 62 patients received commercial supply, 45 had 6 months of follow-up

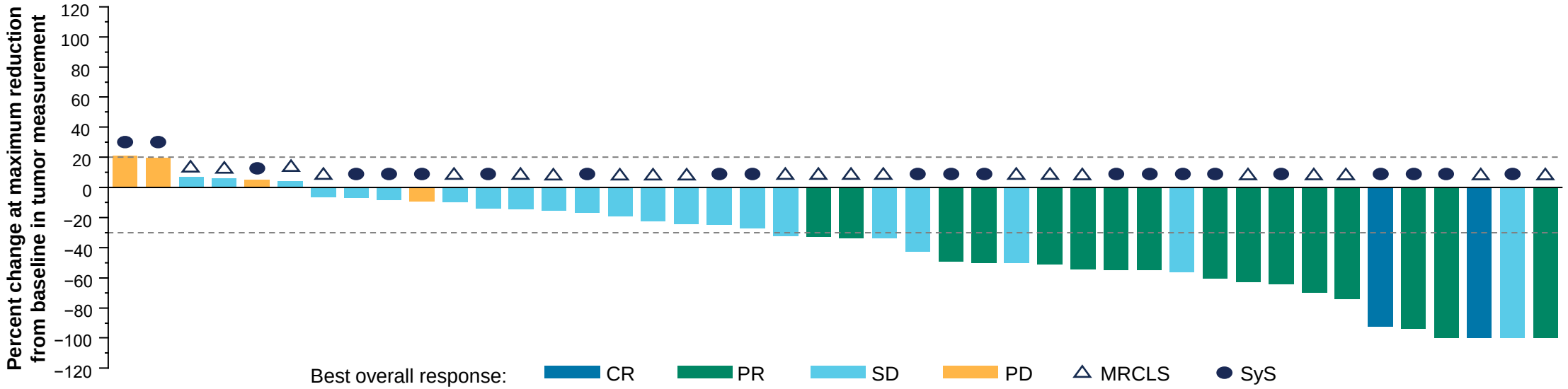
Baseline Characteristics (Efficacy Population)

March 2, 2023, interim analysis

Characteristic	N=45
SyS, n (%)	23 (51)
MRCLS, n (%)	22 (49)
Male, n (%)	25 (56)
Female, n (%)	20 (44)
Race, n (%)	
White	43 (96)
American Indian or Alaska Native	1 (2)
Asian	1 (2)
Age, years, median (min, max)	46 (18, 68)
Extent of disease at screening,[a] n (%)	
Local unresectable	3 (7)
Metastatic	41 (91)

Characteristic	N=45
Systemic therapy regimens before leukapheresis,[b] n (%)	
0	1 (2)
1	10 (22)
2	14 (31)
≥3	20 (44)
Received ifosfamide before leukapheresis, n (%)	34 (76)
Received any anthracycline before leukapheresis, n (%)	44 (98)[b]
Transduced cell dose, median (min, max)	6.4×10^9 (2.1, 11.3)
Continuation of supportive therapy between leukapheresis and lymphodepletion, n (%)	18 (40)
Received a new standard of care between leukapheresis and lymphodepletion, n (%)	5 (11)

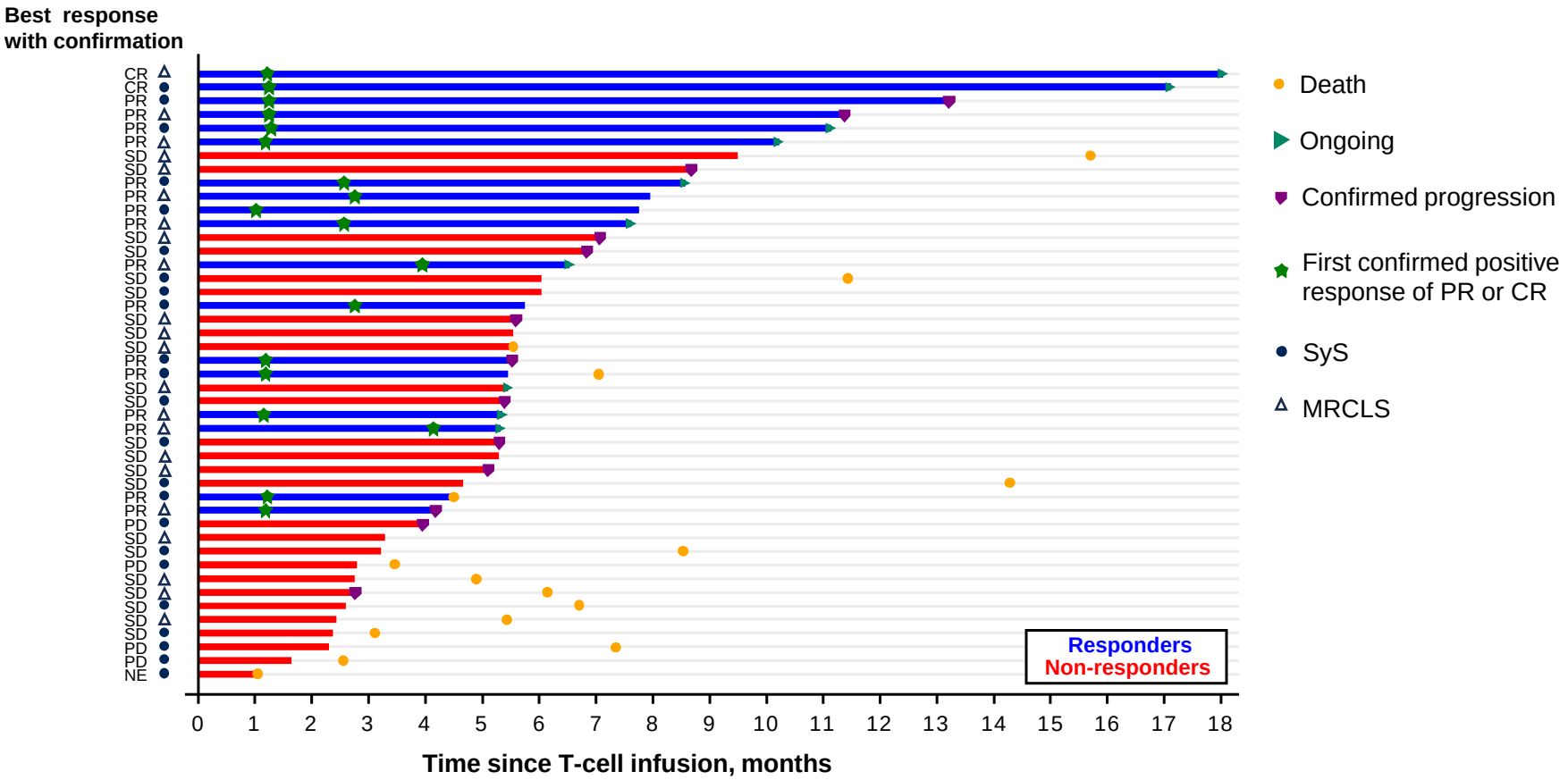
Primary Endpoint (18/45, 40% ORR)



Response Durability

At the data cut (18/45 responses):

- 9 responses were ongoing
- Median duration of response: 10.6 months (95% CI: 3.3–**NE**)



Safety

- **Treatment-emergent lymphodepletion-related AEs of special interest or of any grade in ≥15% of participants (N=73)**

Event	Any grade	Grade ≥3
Any event, n (%)	68 (93)	60 (82)
Neutropenia	47 (64)	46 (63)
Thrombocytopenia	40 (55)	31 (42)
Anemia	34 (47)	23 (32)
Leukopenia	33 (45)	32 (44)
Febrile neutropenia	19 (26)	18 (25)
Alopecia	15 (21)	–
Decreased appetite	15 (21)	2 (3)
Fatigue	14 (19)	2 (3)
Diarrhea	11 (15)	–
Hypokalemia	11 (15)	2 (3)
Rash/rash maculopapular	8 (11)	2 (3)
Lymphopenia	6 (8)	4 (5)

- Safety was assessed in the 73 participants who had received lete-cel
- Two (3%) patients experienced Grade 5 events related to lymphodepletion:
  - Neutropenia was in the setting of pancytopenia, and led to a terminal pulmonary infection
  - Pulmonary alveolar hemorrhage was in the setting of pancytopenia, and a platelet count of 0 despite HLA-matched platelets and platelet-stimulating agents

Conclusions

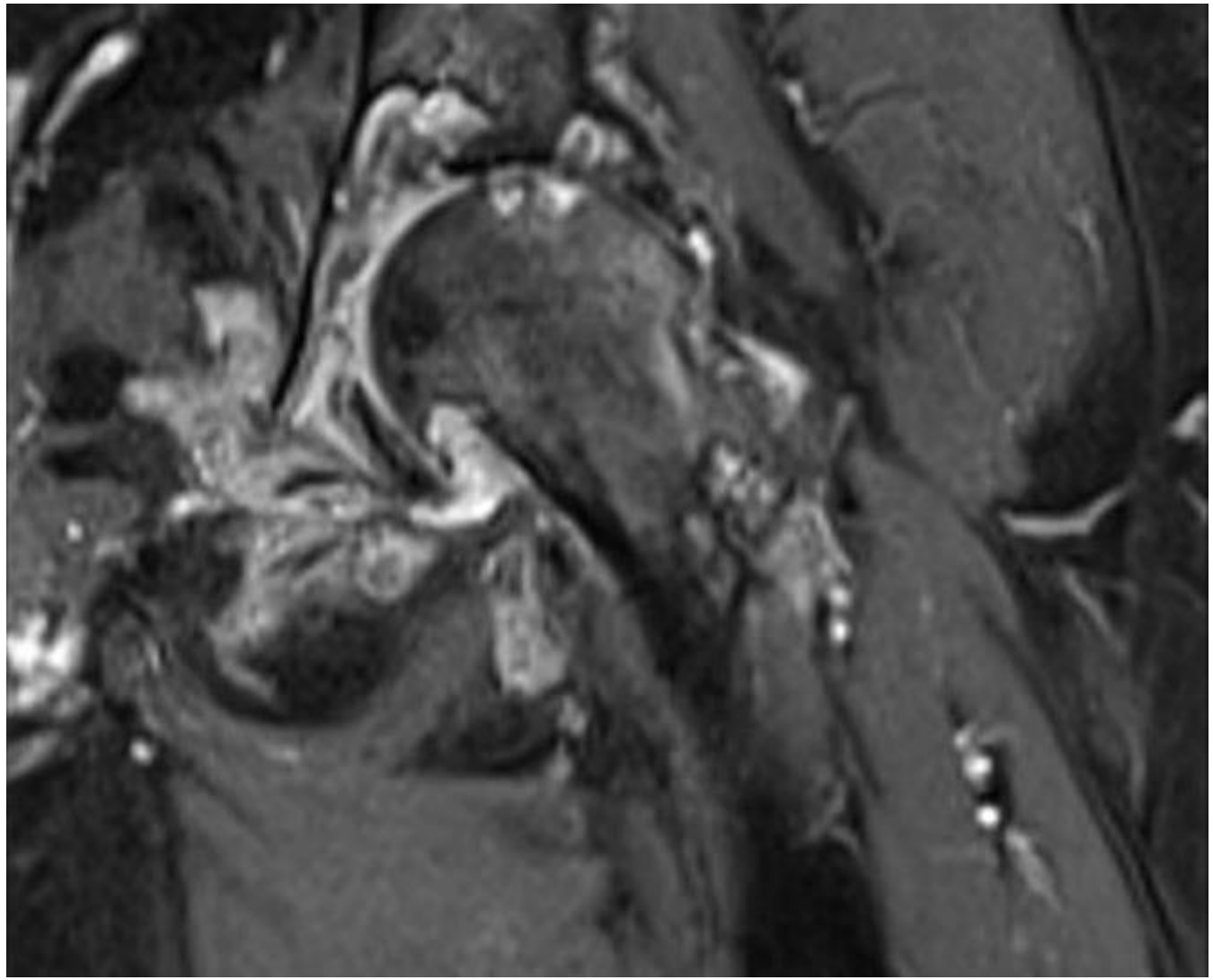
- 40% ORR consistent across synovial sarcoma and myxoid/round cell liposarcoma
- Median duration of response was 10.6 months, with 9 responses ongoing
- Still needs more time to mature
- Will be interesting to compare to recently approved Afamitresgene autoleucel, targeting MAGE-A4

Efficacy, Safety, and Patient-Reported Outcomes of Vimseltinib in Patients with Tenosynovial Giant Cell Tumor: Results From the Phase 3 MOTION Trial

- William D. Tap, Vivek Bhadri, Silvia Stacchiotti, Sebastian Bauer, Andrew J. Wagner, Michiel van de Sande, Nicholas, M. Bernthal, Antonio Lopez Pusa, Albiruni Abdul Razak, Antoine Italiano, Mahbubl Ahmed, Axel Le Cene, Christopher Tait, Fiona Zarins, Brooke Harrow, Maitreyi G. Sharma, Rodrigo Ruiz-Soto, Matthew L. Sherman, Jean-Yves Blay, and Hans Gelderblom, on behalf of the MOTION investigators

Tenysynovial Giant Cell Tumor

- Tenosynovial giant cell tumor (TGCT) is a locally aggressive neoplasm
- Caused by dysregulation of CSF1 gene leading to production of CSF1
- Can involve any joint (knees most common that I see, although can occur in finger joints, hips, spine, TMJ, etc.)
- Results in pain, stiffness, decreased physical function
- Surgery is standard of care, but diffuse subtype has high rate of recurrence and may not be amenable to surgery
- Systemic treatment options include pexidartinib, with significant risk of liver toxicity, and imatinib



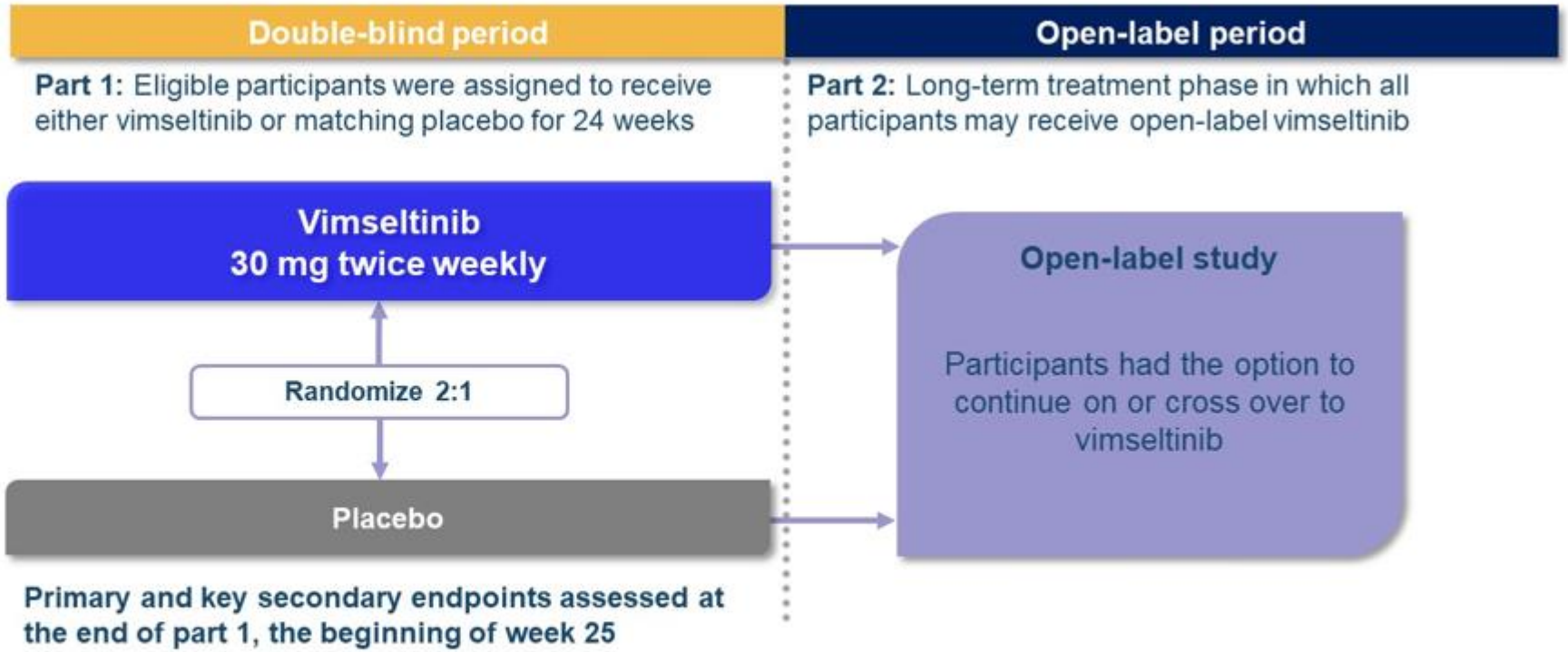
MOTION Trial Design

Key eligibility criteria

Participants ≥18 years old with a confirmed diagnosis of symptomatic TGCT for which surgical resection would potentially cause worsening functional limitation or severe morbidity

Previous treatment with imatinib or nilotinib was allowed

Randomization was stratified by geographical region and tumor location



Primary endpoint: ORR by independent radiological review (IRR) using RECIST v1.1 at week 25
Powered to detect a 30% difference between treatment arms

Endpoints at week 25

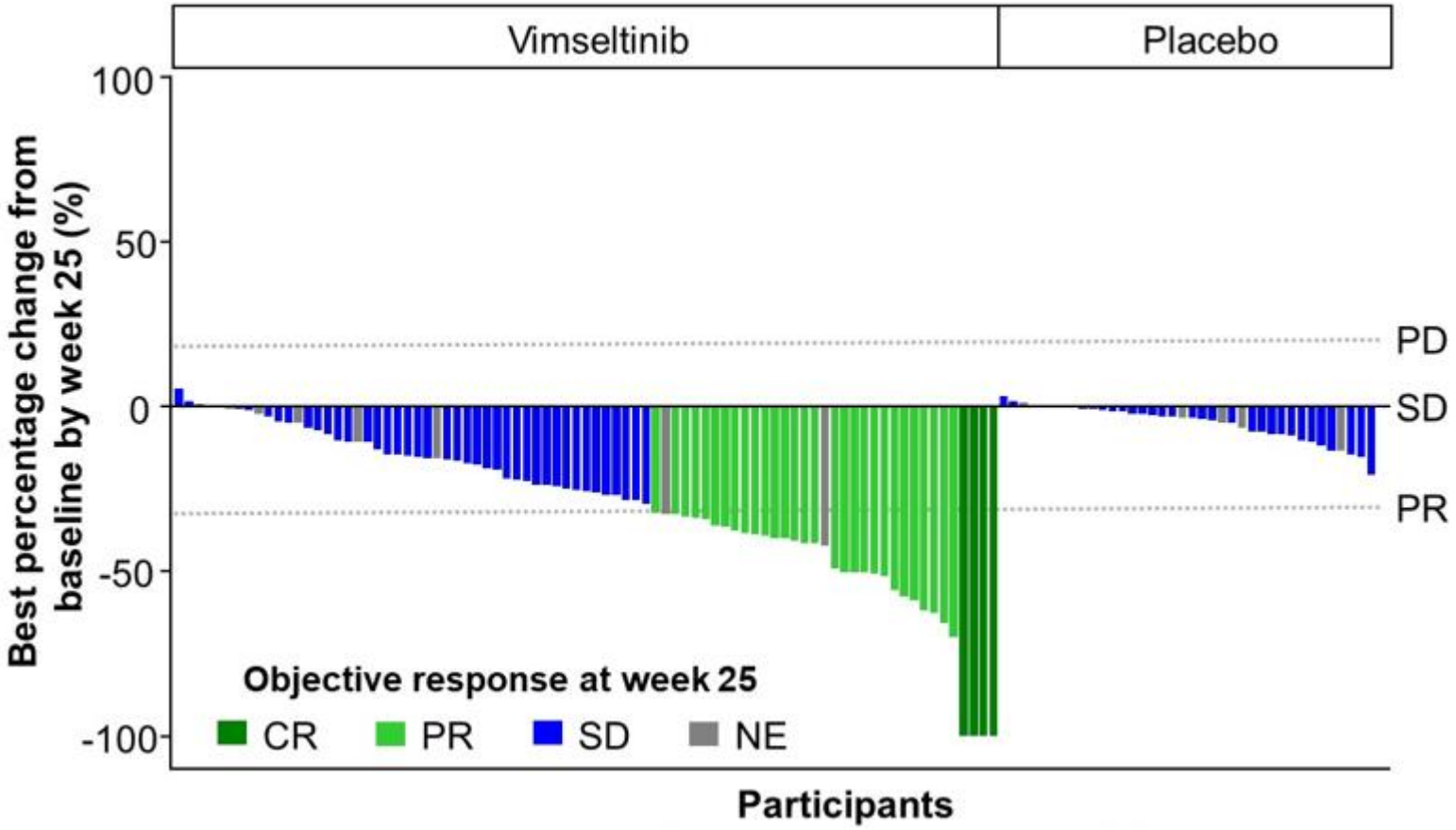
- Primary Endpoint: RESIST 1.1 Criteria
- Secondary endpoints:
  - ORR by IRR using Tumor Volume Score (TVS)
  - Change from baseline in active range of motion (ROM)
  - Patient-reported outcomes
    - PROMIS-physical function questionnaire
    - Stiffness numeric rating scale
    - EQ-Visual Analogue Scale
    - Brief Pain Inventory (BPI) worse pain response rate

Baseline Characteristics

	Vimseltinib n = 83	Placebo n = 40
Age, years, median (IQR)	45 (33–53)	43 (31–53)
Sex		
Female	46 (55)	27 (68)
Male	37 (45)	13 (33)
Race		
White	59 (71)	21 (53)
Asian	1 (1)	4 (10)
Black or African American	4 (5)	0
Other[a]	19 (23)	15 (38)
Affected joint		
Knee	56 (67)	27 (68)
Ankle	9 (11)	6 (15)
Hip	11 (13)	1 (3)
Other[b]	7 (8)	6 (15)
Prior TGCT surgery or procedure[c]	64 (77)	27 (68)
Prior TGCT systemic therapy	19 (23)	9 (23)[d]
Imatinib	16 (19)	7 (18)
Nilotinib	2 (2)	4 (10)
Other[e]	1 (1)	0

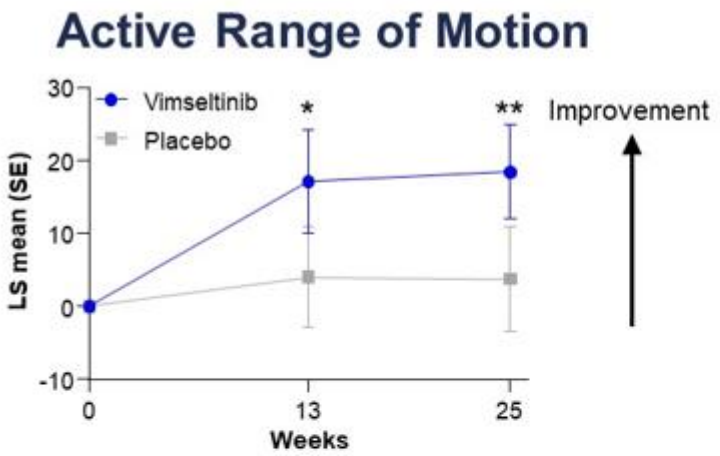
- In the vimseltinib arm, 89% (74/83) of participants completed treatment in part 1
  - Reasons for discontinuations were AE (n = 4), withdrawal by participant (n = 3), and other (n = 2)
- In the placebo arm, 1 participant was randomized to placebo but never received treatment; 87% (34/39) completed treatment in part 1
  - Reasons for discontinuations were withdrawal by participant (n = 3), PD by IRR (n = 1), and physician decision (n = 1)

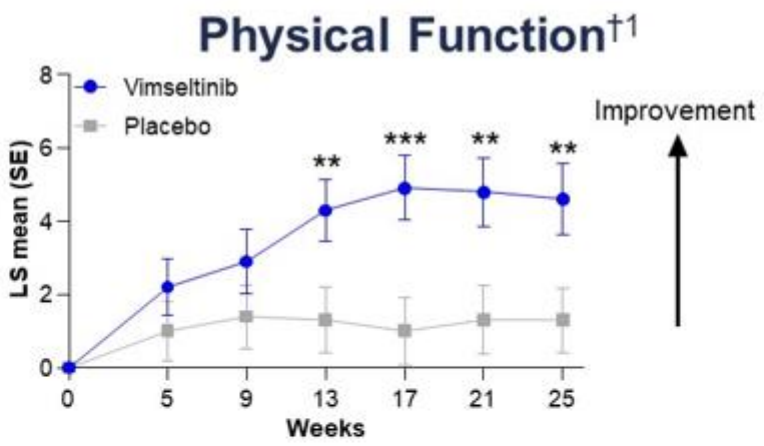
RECIST v1.1

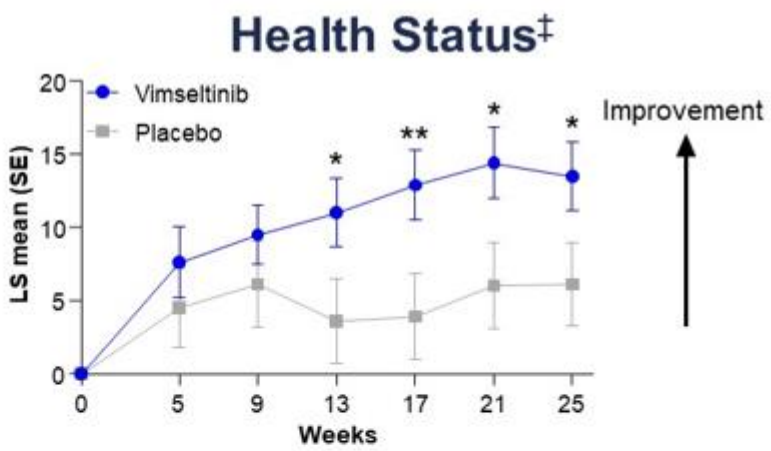


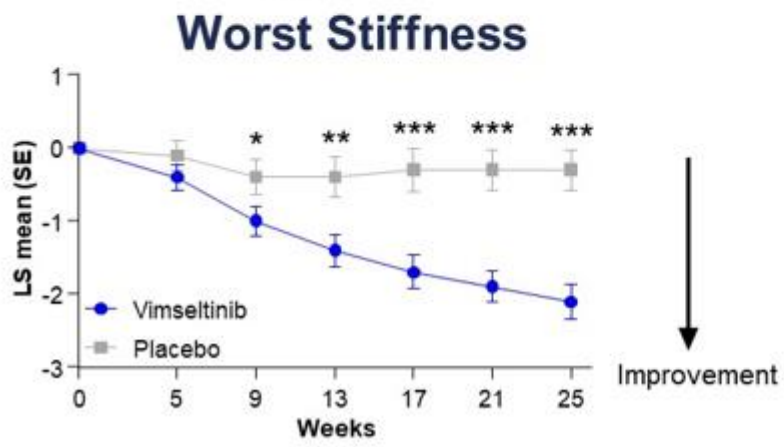
At week 25	Vimseltinib n = 83	Placebo n = 40
Overall response using RECIST v1.1		
CR	4 (5)	0
PR	29 (35)	0
SD	42 (51)	33 (83)
NE	8 (10)	7 (18)
ORR using RECIST v1.1	33 (40)	0
Treatment difference, % (95% CI), *P*-value[a]	40 (29 to 51), ***P* <0.0001**	
DOR using RECIST v1.1, months, median[b] (min, max)	NR (0.03+,11.7+)	N/A

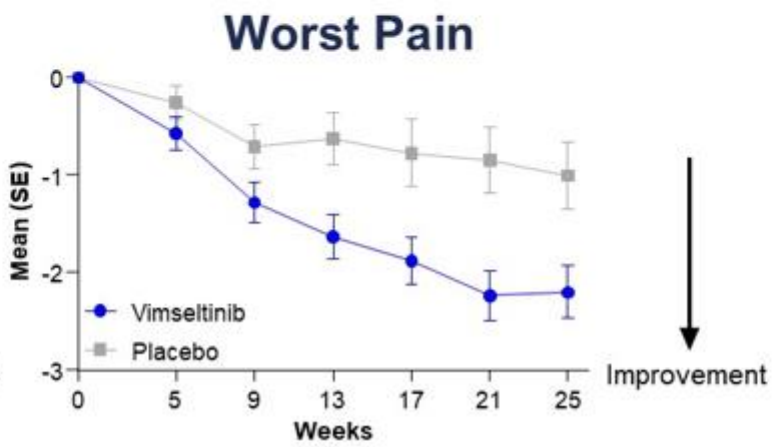
Functional Outcomes











Side Effects

- Periorbital edema (45% all grade, 4% grade 3/4)
- Blood CPK increased (24% all grade, 10% grade 3/4)
  - Not associated with rhabdomyolysis
- AST increase (23%, but no grade 3 or 4)
- Rash (19%)

Conclusions

- Vimseltinib is effective for TGCT, with significant radiologic and (more importantly) symptomatic improvement
- Associated with increase in CPK, which appears to not be associated with rhabdomyolysis
- Less hepatotoxicity

SU2C-SARC032: A Randomized Trial of Neoadjuvant Radiotherapy and Surgery With or Without Pembrolizumab for Soft Tissue Sarcoma

Mowery YM, Ballman K, Hong AM, Schuetze SM, Wager AJ, Monga V, Heise RS, Attia S, Choy E, Burgess MA, Bae S, Pryor D, Van Tine BA, Tinoco G, Chmielowski B, Freeman C, Van de Rijn M, Brigman BE, Riedel RF, Kirsch DG

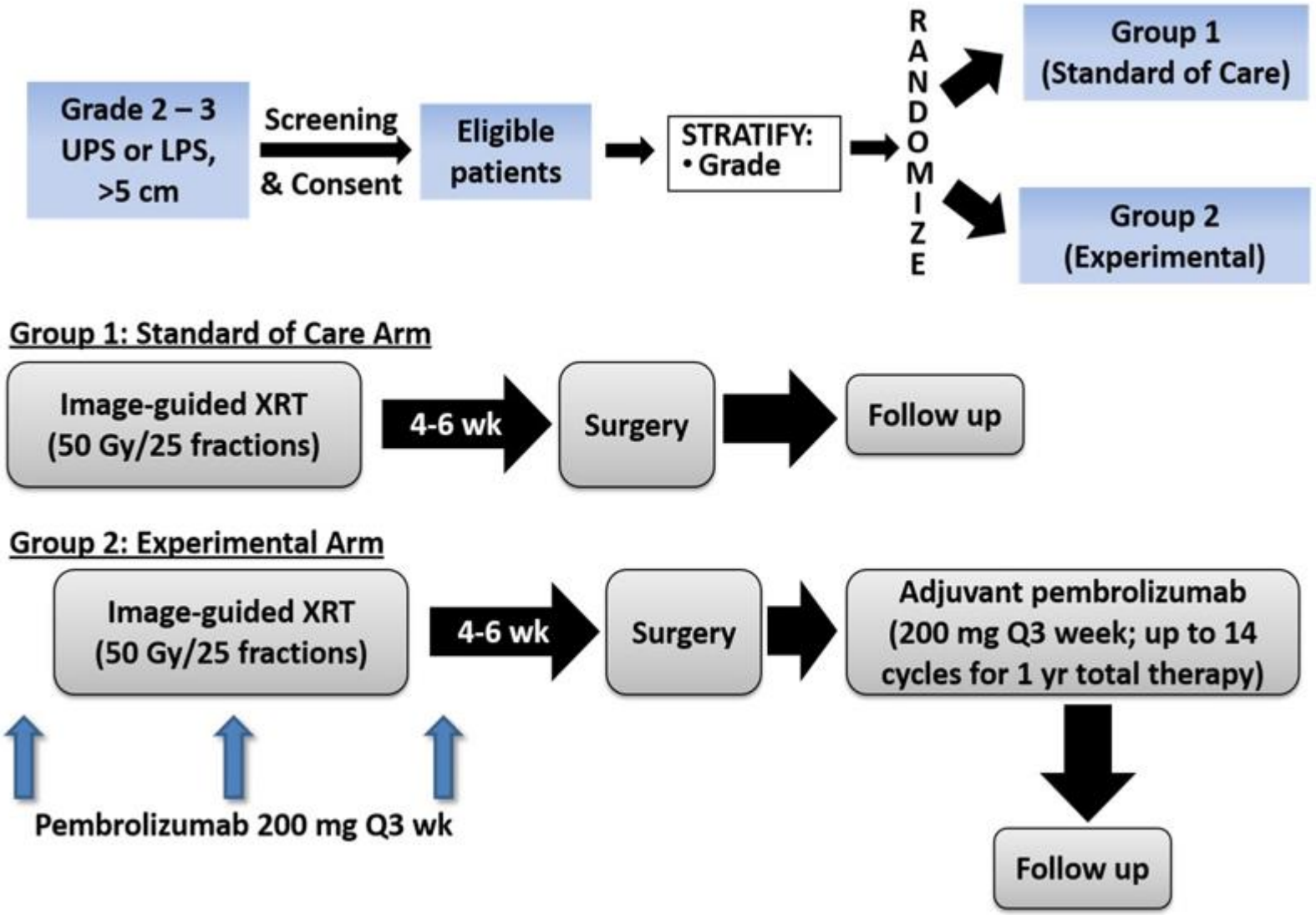
Standard Therapy for Localized Soft Tissue Sarcoma

- Varies, but frequently treated with neoadjuvant radiation followed by surgery, with 90% control
- This is preferred over adjuvant radiation by many centers
- Chemotherapy in neoadjuvant/adjuvant setting not particularly effective except in certain circumstances
- About 50% risk of recurrence for high grade tumors >5 cm

SU2C-SARC032

- Randomized neoadjuvant pembrolizumab with concurrent radiation followed by surgical resection
- Undifferentiated pleomorphic sarcoma and dedifferentiated liposarcoma (felt to be more immunologically sensitive)
- University of Iowa was fourth highest enroller out of twenty sites

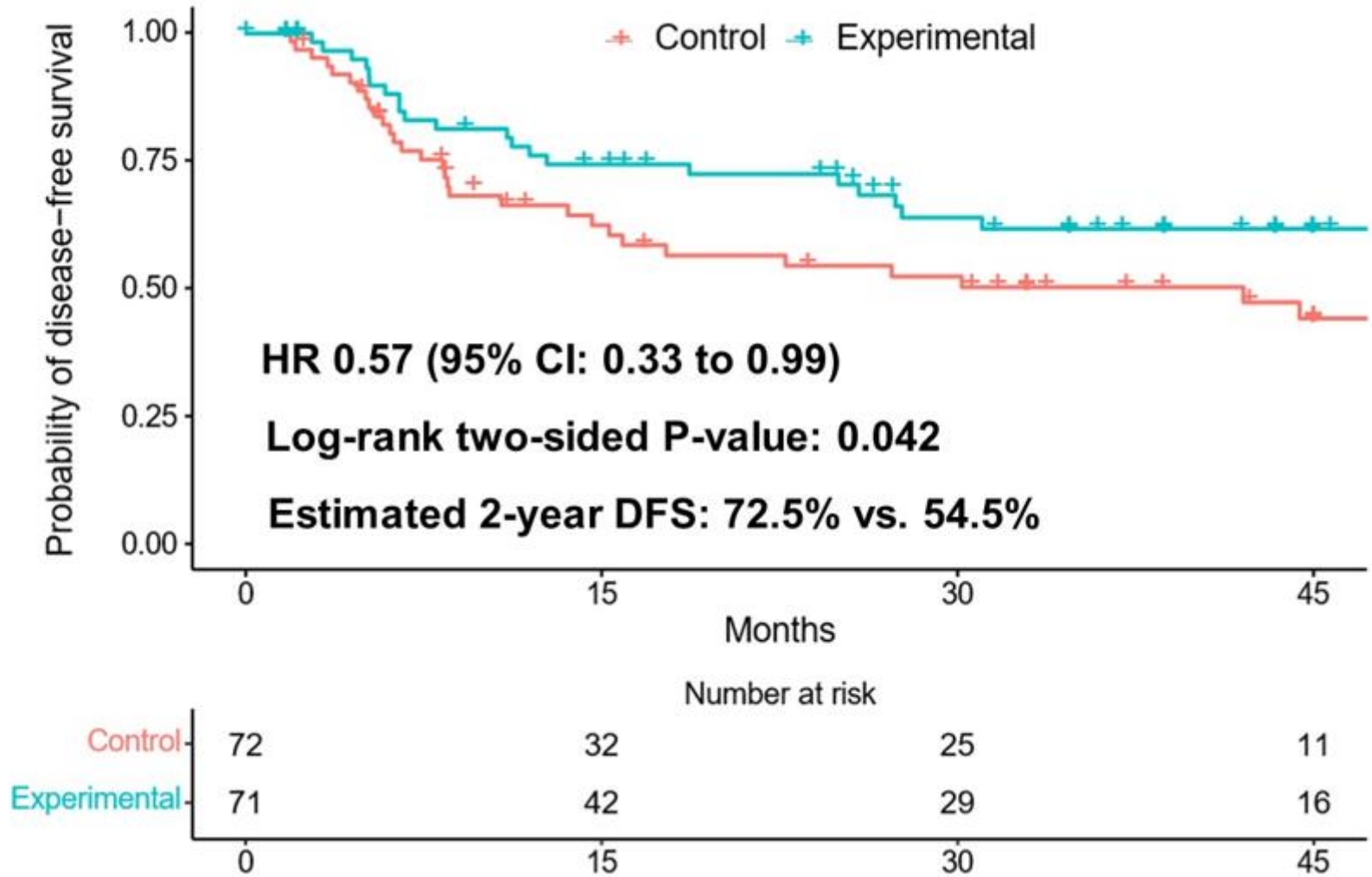
SU2C-SARC032



Baseline Characteristics

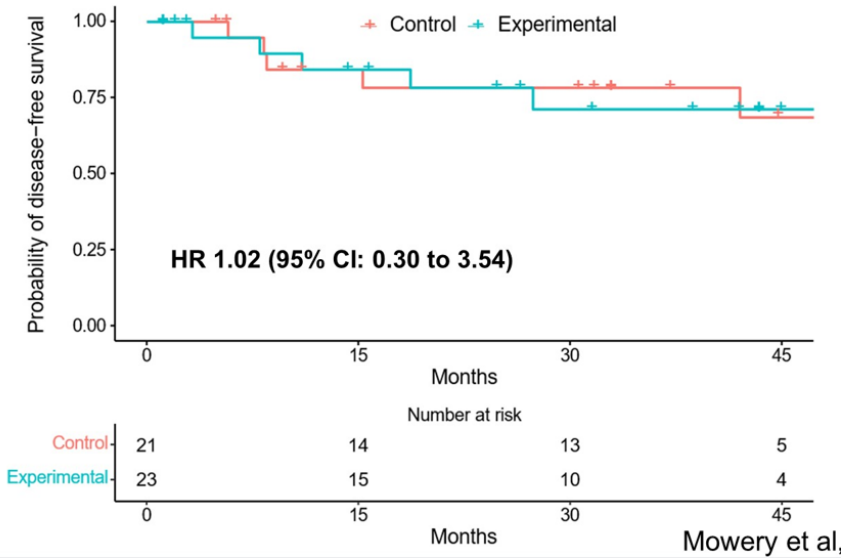
	Control (N=72)	Experimental (N=71)
Sex	N (%)	N (%)
Female	26 (36%)	26 (37%)
Male	46 (64%)	45 (63%)
Grade		
2	25 (35%)	26 (37%)
3	47 (65%)	45 (63%)
Histology		
UPS	60 (83%)	63 (89%)
LPS	12 (15%)	8 (11%)

Intention to Treat Analysis



Grade 2

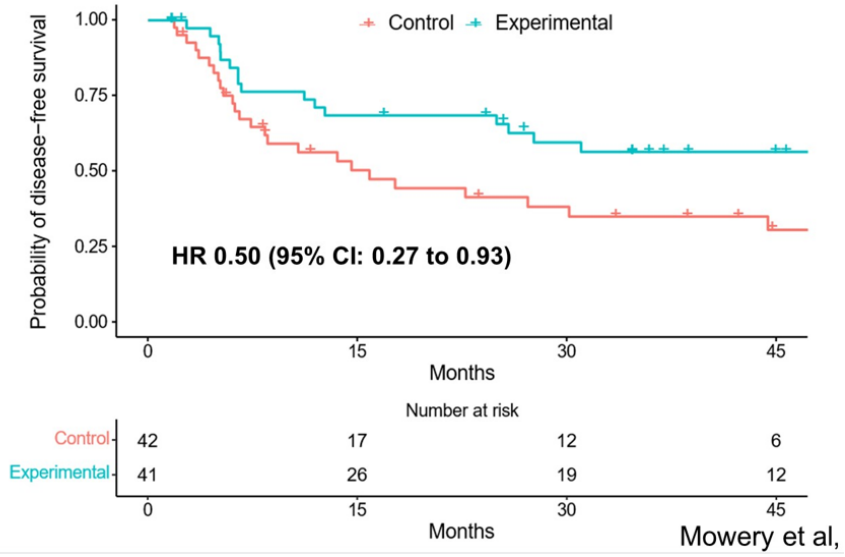
Evaluable Patients



Mowery et al,

Grade 3

Evaluable Patients



Mowery et al,

Safety

- Experimental: 37 of 70 patients (53%)
  - 52% had at least one AE related to pembrolizumab
- Control: 20 of 67 (30%)
- No difference in wound complications
- Most common side effects
  - Dermatitis (radiation) 50%
  - Fatigue 53%
  - Nausea 31%
  - Diarrhea 27%
  - Hypothyroidism 21%

Conclusion

- Addition of pembrolizumab in the neoadjuvant setting improved disease free survival
- Benefits appear to be highest in grade 3, but not powered for subset analysis
- Will likely be a new standard of care for undifferentiated pleomorphic sarcoma

SARC037: Phase II Results of Trabectedin Given as a 1-Hour Infusion in Combination with Low Dose Irinotecan in Patients with Relapsed/Refractory Ewing Sarcoma

Grohar PJ, Ballman KV, Heise R, Mascarenhas L, Glod J, Wedekind MF, Gedminas JM, Dubois SG, Maki RG, Crompton BD, Figg WD, Bagatell R, Laetsch TW, Diamond M, Navid F, Roberts RD Widemann BC, Reinke DK, Chugh R

Ewing's Sarcoma

- Driven by EWS::FLI1 fusion
- First line treatment for localized disease with VAC/IE x 14 cycles with control of the primary works well (~70-80% cure rate)
- First line treatment for metastatic disease works less well (~30% cure rate)
- Treatments in the second line setting are not particularly effective
- Mechanistic data suggests that concentration of trabectedin needs to be higher to inhibit EWS::FLI1, which can be done with a one hour infusion

SARC037

- Single arm phase II design
- Multicenter study
- Trabectedin 1 mg/m2 IV over 1 hour D1
- Irinotecan 25 mg/m2 IV day 2, 4

- Eligibility
  - Age >6 years
  - Ewing's sarcoma

Objectives

- Primary Objective
  - ORR per RECIST v1.1 (successful if 4 of 18 patients respond)
- Secondary Objective
  - PFS
  - 6 month PFS
  - Safety and tolerability
- Exploratory Objective
  - EWS::FLI1 transcriptional networks
  - ctDNA, CTCs, Tumor Profiling

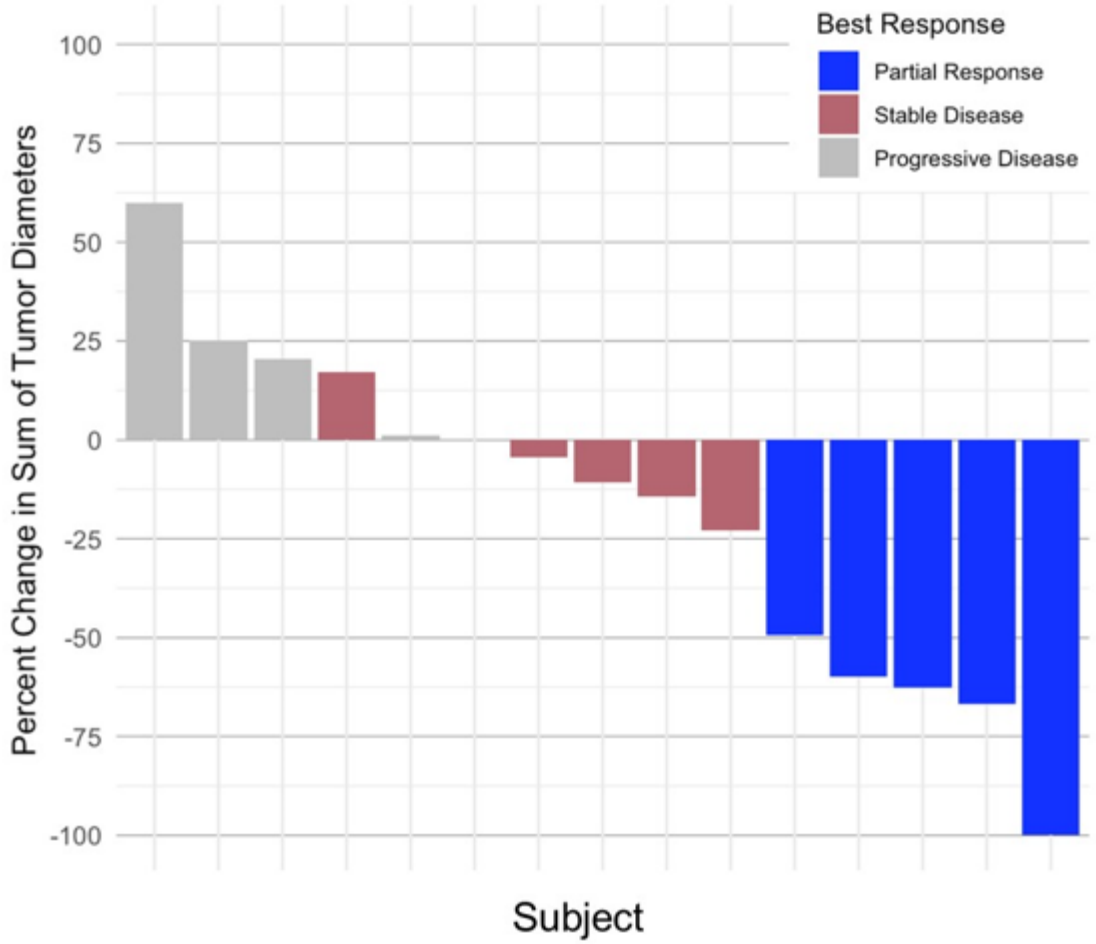
Demographics

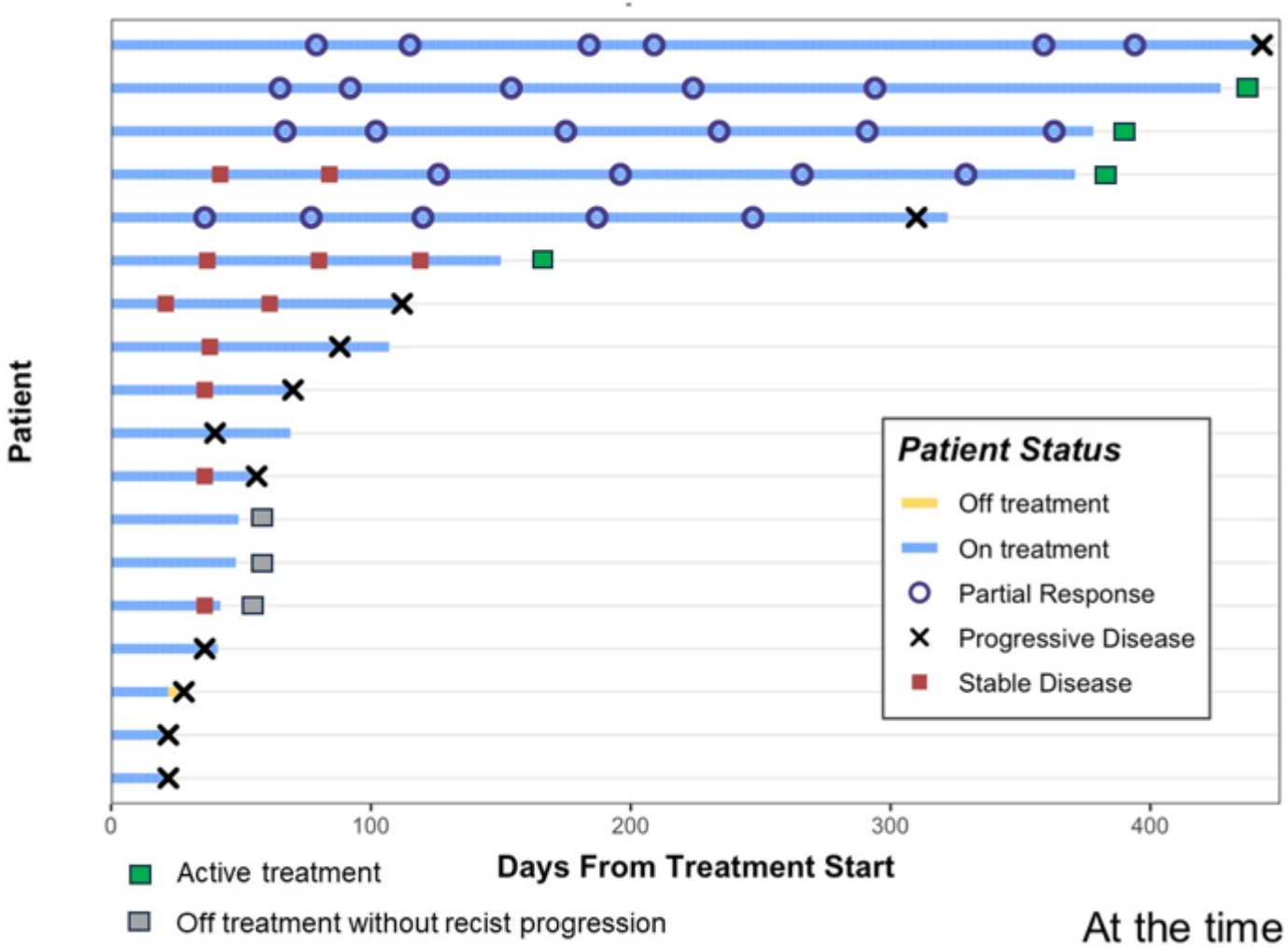
18 patients enrolled
6 institutions

Characteristic	No. (%)	Characteristic	No (%)
Age		Prior Lines of Therapy	
Median (Range)	21 (9-43)	Median (Range)	4 (1-7)
Age at Diagnosis		Prior Irinotecan	
Median (Range)	17 (3-39)	Yes	12 (67%)
Gender		Prior Radiation	16 (89%)
Male	10 (56%)	Lung	9 (50%)
Female	8 (44%)	Pelvis	7 (39%)
Race		Primary Tumor Site	
Asian	1 (6%)	Abdomen	3 (18%)
Black	1 (6%)	Extremity	4 (22%)
Latino/a/x or hispanic	3 (17%)	Head and neck	1 (6%)
Middle Eastern Northern African	1 (6%)	Pelvis	3 (17%)
White	12 (67%)	Skin	1 (6%)
Ethnicity		Spine	1 (6%)
Hispanic	4 (22%)	Other	5 (28%)

For 50% of patients SARC037 was 5th regimen

Demographics





2.9 mos. PFS

Median time to response (months)

- 2.60 (2.17 to 3.81)

Median duration of response (months):

- 7.53 (6.94 to 9.73)

Progression-free survival rate

- 4.5 mos: 47% (95% CI, 28 to 81)
- 6 mos: 40% (95% CI, 21 to 75)

At the time of data cutoff 5/2024; 4 patients remain on study

Conclusion

- Promising phase II trial in highly pretreated patients, with fairly long PFS in responding patients
- Very small study
- Will need to expand study to determine true efficacy


Questions

Works Cited

D'Angelo SP, Furness AJ, Thistlethwaite F, Burgess MA, Riedel RF, Haanen J, Noujaim J, Chalmers AW, Pousa AL, Chugh R, Davis LE. Lete-cel in patients with synovial sarcoma or myxoid/round cell liposarcoma: Planned interim analysis of the pivotal IGNYTE-ESO trial.

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Tap WD, Bhadri V, Stacchiotti S, Bauer S, Wagner AJ, van de Sande M, Bernthal NM, López Pousa A, Abdul Razak AR, Italiano A, Ahmed M. Efficacy, safety, and patient-reported outcomes of vimseltinib in patients with tenosynovial giant cell tumor: Results from the phase 3 MOTION trial.